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New chiral ligands from isosorbide: application in asymmetric transfer hydrogenation

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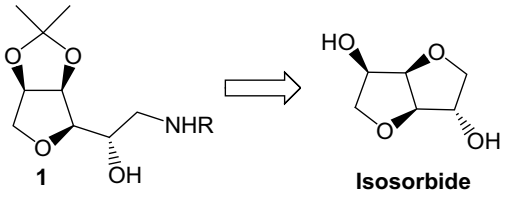
ABSTRACT

New chiral β-amino alcohols have been designed and synthesized from isosorbide, a by-product from the starch industry. These new ligands have been synthesized in three steps from isosorbide in good yields and have been used in asymmetric transfer hydrogenation reaction with Ru^{II} complexes. One of these catalysts also demonstrated good catalytic activity and good enantioselectivity.

1. Introduction

Asymmetric catalysis is one of the most promising methods for the synthesis of chiral compounds. Among the enantioselective catalytic reactions promoting formation of important chiral building blocks, asymmetric reduction of prochiral ketones is one of the most studied reactions. Although enantioselective hydrogenation[1] or borane reductions[2] are generally efficient to form enantiomerically pure secondary alcohols, they require the use of either high pressure or hazardous reagents and air-sensitive catalysts. An alternative method is the asymmetric transfer hydrogenation reaction using mainly 2-propanol as the hydrogen source under mild reaction conditions in the presence of Ru, Rh, or an Ir-based catalyst.[3] Furthermore, 2-propanol is a non-toxic, inexpensive, easy and safe to handle and an environmentally friendly hydrogen donor. The first chiral ligands employed in this asymmetric reduction were chiral phosphines (DIOP,[4] BINAP[5] CHIRAPHOS[6]), but since the beginning of the 1990s, chiral bidentate nitrogen ones have been mainly used. Later, Noyori et al. reported the use of chiral monotosylated diamine/Ru(II)-complexes.[7] They also showed that the use of β-amino alcohols as a ligand could accelerate the reaction rate.[8] Moreover, as a little modification on the structure of the ligand generally has a strong effect on the activity and the selectivity of the catalyst, many research groups further developed β-amino alcohol-based catalysts.[9] Furthermore, to the best of our knowledge, no carbohydrate-derived β-amino alcohols have been used as ligands in the asymmetric transfer hydrogenation reaction.

As part of an ongoing program aimed at finding an efficient system for the asymmetric transfer hydrogenation reaction, we were interested by the utilization of biomass products, particularly isosorbide. Isosorbide is a by-product from the starch industry formed by the dehydration of sorbitol. Although isosorbide is commercially available, their derivatives have been extensively employed in medicine as vasodilators[10] and factor Xa inhibitors[11] or in the syntheses of biodegradable polymers.[12] Few have been applied as chiral auxiliaries[13] as starting materials for a chiral phase-transfer catalyst[14] or as chiral amino alcohols.[15]



Scheme 1. New chiral β-amino alcohols **1** from isosorbide.

Herein, we report the rapid synthesis of new chiral β-amino alcohols **1** from isosorbide (Scheme 1) along with the preliminary results concerning their use as ligands for the Ru^{II}-catalyzed asymmetric hydrogen transfer reduction of acetophenone.

2. Results and discussion

2.1. Synthesis of chiral ligands

A few years ago, we reported the synthesis of epoxide **2** in two steps from isosorbide.[16] The ring-opening of the oxirane group of compound **2** with 2 equiv of primary amines led to β-amino alcohols **1** in moderate to excellent yields after column chromatography (Scheme 2), (Table 1, entries 1–4 and 7–11).

Moreover, in order to perform the ring-opening reaction with methylamine, a volatile reagent, the reaction was carried out with a large excess of methylamine (40% aqueous solution) in dichloromethane at room temperature. The resulting product **1f** was formed in 62% yield (Table 1, entry 6).

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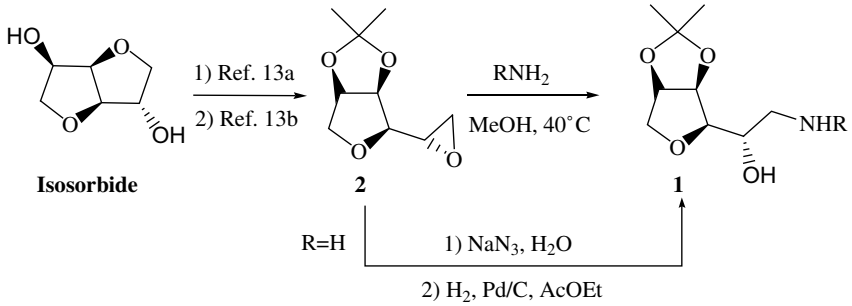
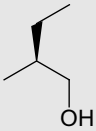
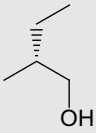


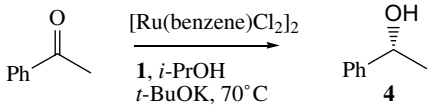
Scheme 2. Synthesis of chiral amino alcohols **1** from isosorbide.

Table 1
β-Amino alcohols **1a–k** produced via Scheme 2

Entry	R	Ligand	Yield[a] (%)
1	$PhCH_2$	**1a**	66
2		**1b**	80
3		**1c**	95
4	Ph	**1d**	75
5	H	**1e**	85
6	Me	**1f**	62
7	*i*-Pr	**1g**	77
8	Cyclohexyl	**1h**	85
9	*t*-Bu	**1i**	69
10		**1j**	75
11		**1k**	95
12	Amine: 	**1l**	98

[a] Isolated yield after column chromatography.

Table 2
Asymmetric transfer hydrogenation of acetophenone using ligands **1**[a]



Entry	Ligand	Time (h)	Conversion[b] (%)	ee[b] (%) (Config.[c])
1	**1a**	21	96	60 (*R*)
2[d]	**1b**	21	83	21 (*R*)
3[d]	**1c**	21	90	18 (*R*)
4	**1d**	21	66	20 (*R*)
5	**1e**	21	72	64 (*R*)
6	**1f**	21	48	<5
7	**1g**	21	83	30 (*R*)
8	**1h**	21	86	6
9	**1i**	21	67	—
10	**1j**	21	28	24 (*R*)
11	**1k**	21	10	—
12	**1l**	21	38	—
13	**1a**	3	95	47 (*R*)
14[d]	**1a**	3	95	57 (*R*)
15[e]	**1a**	3	58	78 (*R*)
16[d,f]	**1a**	3	85	74 (*R*)
17[d,f]	**1a**	42	92	70 (*R*)

[a] Asymmetric reduction of acetophenone was carried out in a 0.2 M solution in 2-propanol with [acetophenone]/[*t*-BuOK]/[Ligand]/[Ru] = 100/1.5/1.5/1.
[b] Determined by chiral GC analysis.
[c] Assigned by comparison of the specific rotation with literature values.
[d] [acetophenone]/[*t*-BuOK]/[Ligand]/[Ru] = 100/2/2/1.
[e] [acetophenone]/[*t*-BuOK]/[Ligand]/[Ru] = 100/4/4/1.
[f] Reaction was carried out at 25 °C.

Transformation of epoxide **2** to β-amino alcohol **1e** bearing a primary amino function was performed with sodium azide in water, followed by reduction of the azide (overall yield: 85%) (Scheme 2), (Table 1, entry 5).

β-Amino alcohol **1l**, bearing a morpholino moiety, was obtained in a 98% yield (Table 1, entry 12) with 1 equiv of morpholine in methanol at 40 °C.

2.2. Asymmetric transfer hydrogenation reaction

These β-amino alcohols **1** were then evaluated for the asymmetric transfer hydrogenation reaction of acetophenone (Table 2).

In a typical experiment, ruthenium complexes were prepared in situ by refluxing 0.5 mol % of $[RuCl_2(benzene)]_2$ with 1.5 mol % of the β-amino alcohols in isopropanol at 70 °C for 1 h. The resulting solution was then used to reduce acetophenone in the presence of a 1.5 mol % of *tert*-butoxide (0.1 M) in isopropanol at 70 °C for 21 h, using a substrate/catalyst ratio of 100.

Ligands **1a**, **1b**, and **1c** derived from benzylamines (Table 2 entries 1–3) gave the best conversions of up to 80% but the absence or the presence of a methyl group on the benzylic position had a drastic effect on the enantioselectivity. With α-methylbenzylamine derivatives **1b** and **1c** (entries 2 and 3), enantioselectivities of the reduction did not exceed 21%, contrary to that with benzylamine (60% ee).

Moreover, no match/mismatch effects were found contrary to what Patti et al. observed with chiral equivalent β-amino alcohols in the ferrocenyl series.[9p]

The reaction with the aniline-derived β-amino alcohol **1d** was also performed but both conversion and ee were low (Table 2, entry 4).

For ligand **1e** with a primary amine, although the conversion was moderate, a similar level of enantioselectivity as for β-amino alcohol **1a** was found (Table 2, entry 5). For ligands **1f–1i** with an alkylamine moiety (Table 2, entries 6–9), various outcomes have been observed. Surprisingly, the combination of ligand **1f** with Ru^{II} did not reduce acetophenone efficiently (entry 6). Furthermore, it seems that introduction of a group at the α-position of the nitrogen atom has an influence on the enantioselectivity and sometimes on

the reaction rate. Indeed, as in entries 2 and 3, a similar conversion range was observed with ligands **1g** and **1h** containing a secondary carbon at the α-position of the nitrogen atom (entries 7 and 8). The best stereoinduction was detected with ligand **1g**. β-Amino alcohol **1i** with a bulky group on the nitrogen atom was less efficient in terms of catalytic activity (67% conversion) and no asymmetric induction was observed (entry 9). The same outcome was observed by Carpentier et al. with an ephedrine series.[9j]

Tridentate ligands **1j** and **1k** were not very efficient; however, a slight match/mismatch effect was observed in these cases (Table 2, entries 10 and 11).

We also checked the effect of ligand **1l** containing a tertiary amine. The conversion was low and 1-phenylethanol was obtained as a racemic mixture (Table 2, entry 12). Different research groups have pointed out that these type of ligands were not efficient for the asymmetric transfer hydrogenation reaction.[17]

Different investigations were then focused on the Ru^{II}–**1a** catalyst to find the optimum conditions for the asymmetric transfer hydrogenation of acetophenone by changing the reaction time, the Ru^{II}/**1a**/base ratio, or the temperature (Table 2, entries 13–17). When the reaction time was reduced to 3 hours, we noticed a decrease of the enantioselectivity (entries 1 and 13). The higher the Ru^{II}/**1a**/base ratio, the higher the enantioselectivity, but the lower the conversion (entries 13–15). As expected, decreasing the temperature to room temperature enhances the enantioselectivity with a slight drop in the catalytic activity (entries 15 and 16). A longer reaction time of 42 h did not significantly change the enantioselectivity but the conversion rose to 92% (entries 16 and 17).

3. Conclusion

In conclusion, we have developed the synthesis of new chiral carbohydrate-derived β-amino alcohols. These ligands were obtained in moderate to excellent yields. For the first time, we have shown that carbohydrate-derived β-amino alcohols could be used as ligands for the asymmetric hydrogen transfer reaction of acetophenone. The conversion of acetophenone into 1-phenylethanol was low to high (10–95%), while enantioselectivity (0–78%) is highly dependant on the β-amino alcohol ligand structure. The chiral amino alcohol **1a** proved to be the most efficient ligand in the series examined for the Ru^{II}-catalyzed asymmetric reduction of acetophenone.

Studies are currently in progress in order to improve the enantioselectivity, and other substrates have to be tested to screen the scope and limitations of these new catalytic systems.

4. Experimental

4.1. General

Moisture or air-sensitive reactions were conducted under an atmosphere of argon in oven-dried glassware. The asymmetric transfer hydrogenation reactions were performed in a dried and degassed Schlenk tube, and solvents and reagents were also degassed prior to use.

All anhydrous solvents were distilled calcium hydride (acetone, acetonitrile, and isopropanol) and stored under an argon atmosphere. Reactions were monitored by TLC (Macherey–Nagel Polygram®sil G/UV_{254}). Column chromatography was performed on silica gel (Merck, 230–400 mesh).

400 MHz ^{1}H NMR spectra and 100.6 MHz ^{13}C spectra were recorded on a Bruker AC-400 in $CDCl_3$. ^{1}H and ^{13}C chemical shifts are expressed as parts per million downfield from the internal standards tetramethylsilane for $CDCl_3$ solutions. Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), or br s (broadened singlet). FT-IR spectra were performed on an ATR Perkin–Elmer Spectrum one apparatus and only major band positions are given in cm^{-1}. Optical rotations were recorded on a Perkin–Elmer 343 polarimeter at 25 °C. High resolution mass spectra were performed on a Waters Micromass® GCT Premier™ apparatus (oa-TOF) in CI mode. Elemental analyses have been done at the Institut de Chimie des Substances Naturelles in Gif-sur-Yvette, France.

Conversions and enantiomeric excesses for the catalytic asymmetric reactions were determined by GC (Hewlett Pakard 6890 equipped with a FID) on a chiral Restek β-dex sm™ column. Melting points were measured on a Buchi B-540 apparatus and were uncorrected.

4.2. General procedure for synthesis of chiral β-amino alcohols 1

A solution of epoxide **2** (1 equiv) and amine (2 equiv) was heated at 60 °C in methanol (C = 0.2 M) for 16 h. The solvent was then removed and the crude product was purified by column chromatography.

4.2.1. 3,6-Anhydro-1-(benzylamino)-1-deoxy-4,5-*O*-isopropylidene-D-sorbitol 1a

Yield: 66%; white solid; mp 66–71 °C; $[\alpha]_D = -57.5$ (c 1.0, CH_2Cl_2); R_f = 0.22 (eluent: CH_2Cl_2/MeOH (95/5)). IR 3423, 3314, 2980, 2941, 2856, 1600, 1496, 1463, 1371, 1342, 1167, 1140, 1106. ^{1}H NMR: δ 1.30 (s, 3H), 1.48 (s, 3H), 2.25 (br s, 2H), 2.79 (dd, 1H, J = 12.2, 7.8 Hz), 2.91 (dd, 1H, J = 12.2, 3.8 Hz), 3.39 (dd, 1H, J = 6.3, 3.5 Hz), 3.48 (dd, 1H, J = 10.7, 3.8 Hz), 3.78 (d, 1H, J = 13.2 Hz), 3.64 (d, 1H, J = 13.2 Hz), 4.01 (d, 1H, J = 10.7 Hz), 4.13 (ddd, 1H, J = 7.8, 6.3, 3.8 Hz), 4.64 (dd, 1H, J = 6.0, 3.5 Hz); 4,77 (dd, 1H, J = 6.0, 3.8 Hz), 7.10–7.30 (m, 5H). ^{13}C NMR: δ 24.9, 26.4, 51.3, 54.0, 69.8, 73.0, 80.9, 81.6, 84.3, 112.5, 127.3, 128.7, 129.2, 140.5. Anal. Calcd for $C_{16}H_{22}NO_4$: C, 65.51; H, 7.90; N, 4.77. Found: C, 65.64; H, 7.99; N, 4.69.

4.2.2. 3,6-Anhydro-1-((*R*)-α-methylbenzylamino)-1-deoxy-4,5-*O*-isopropylidene-D-sorbitol 1b

Yield: 80%; white solid; mp 81–84 °C; $[\alpha]_D = -17.3$ (c 1.0, CH_2Cl_2); R_f = 0.20 (eluent: CH_2Cl_2/MeOH (95/5)). IR 3400, 3334, 3200, 2934, 2845, 1455, 1380, 1372, 1205, 1165, 1103, 1057. ^{1}H NMR: δ 1.27 (s, 3H), 1.38 (d, 3H, J = 6.6 Hz), 1.46 (s, 3H), 2.0–2.5 (br s, 2H), 2.6–2.8 (m, 2H), 3.33 (dd, 1H, J = 5.6, 3.5 Hz), 3.44 (dd, 1H, J = 10.7, 3.7 Hz), 3.78 (q, 1H, J = 6.6 Hz), 4.0–4.1 (m, 2H), 4.63 (dd, 1H, J = 6.0 Hz, J = 3.5 Hz), 4.75 (dd, 1H, J = 6.0, 3.7 Hz), 7.1–7.3 (m, 5H). ^{13}C NMR: δ 24.7, 24.9, 26.3, 50.4, 58.9, 69.9, 70.0, 81.3, 81.7, 83.7, 112.2, 127.0, 127.3, 128.8, 146.1. Anal. Calcd for $C_{17}H_{25}NO_4$: C, 66.43; H, 8.20; N, 4.56. Found: C, 66.09; H, 8.06; N, 4.42.

4.2.3. 3,6-Anhydro-1-((*S*)-α-methylbenzylamino)-1-deoxy-4,5-*O*-isopropylidene-D-sorbitol 1c

Yield: 95%; white solid; mp 102–105 °C; $[\alpha]_D = -90.0$ (c 1.0, CH_2Cl_2); R_f = 0.4 (eluent: CH_2Cl_2/MeOH (95/5)). IR 3443, 3314, 2973, 2937, 2861, 1492, 1474, 1453, 1380, 1342, 1203, 1167, 1151, 1107, 1093, 1051. ^{1}H NMR: δ 1.26 (s, 3H), 1.37 (d, 3H, J = 6.5 Hz), 1.46 (s, 3H), 1.8–2.4 (br s, 2H), 2.55 (dd, 1H, J = 12.2, 7.9 Hz), 2.79 (dd, 1H, J = 12.2, 3.6 Hz), 3.35 (dd, 1H, J = 6.3, 3.6 Hz), 3.46 (dd, 1H, J = 10.8, 3.5 Hz), 3.80 (q, 1H, J = 6.5 Hz), 4.0–4.1 (m, 1H), 4.04 (d, 1H, J = 10.8 Hz), 4.52 (dd, 1H, J = 6.0, 3.6 Hz), 4.74 (dd, 1H, J = 6.0, 3.5 Hz), 7.2–7.4 (m, 5H). ^{13}C NMR: δ 24.4, 24.5, 25.9, 49.1, 57.9, 69.0, 72.6, 80.4, 81.1, 83.6, 112.0, 126.6, 126.8, 128.3, 145.3. Anal. Calcd for $C_{17}H_{25}NO_4$: C, 66.43; H, 8.20; N, 4.56. Found: C, 66.26; H, 8.11; N, 4.37.

4.2.4. 3,6-Anhydro-1-(benzeneamino)-1-deoxy-4,5-*O*-isopropylidene-D-sorbitol 1d

Yield: 75%; slightly yellow oil; $[\alpha]_D = -70.0$ (*c* 0.25, CH_2Cl_2); $R_f = 0.76$ (eluent: CH_2Cl_2/MeOH (9/1)). IR 3394, 3052, 2985, 2936, 1602, 1507, 1456, 1380, 1372, 1267, 1207, 1095. ^{1}H NMR: δ 1.34 (s, 3H), 1.51 (s, 3H), 2.9–3.1 (br s, 2H), 3.27 (dd, 1H, *J* = 12.8, 7.1 Hz), 3.45 (dd, 1H, *J* = 12.8, 4.2 Hz), 3.47–3.53 (m, 2H), 4.10 (d, 1H, *J* = 10.8 Hz), 4.24–4.29 (m, 1H), 4.70 (dd, 1H, *J* = 6.2, 3.7 Hz), 4.81 (dd, 1H, *J* = 6.2, 3.7 Hz), 6.68–6.76 (m, 3H), 7.14–7.21 (m, 2H). ^{13}C NMR: δ 24.5, 25.9, 46.2, 68.9, 72.5, 80.9, 81.4, 83.0, 112.4, 113.2, 117.6, 129.2, 129.3, 148.2. HRMS (CI) calcd for $C_{15}H_{22}NO_4$ $(M+H)^+$, 280.1549; found, 280.1553.

4.2.5. 3,6-Anhydro-1-amino-1-deoxy-4,5-*O*-isopropylidene-D-sorbitol 1e

A solution of epoxide **2** (1.86 g; 10 mmol) and sodium azide (3.25 g; 50 mmol) in water (20 mL) was stirred at 30 °C for 14 h. The solution was extracted twice with diethyl ether and the organic layer was dried over $MgSO_4$. Evaporation of the solvent led to an azide which was used without further purification and dissolved in ethyl acetate. Pd/C 5% (60 mg) was then added and the mixture was stirred in presence of H_2 (4.5 bars) for 2 days. After filtration, the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography to lead to **1e**. Yield: 85% (1.73 g); white solid; mp 82–84 °C; $[\alpha]_D = -40.0$ (*c* 1.0, CH_2Cl_2); $R_f = 0.05$ (eluent: CH_2Cl_2/MeOH (9/1)). IR 3328, 2998, 2933, 2847, 1564, 1424, 1372, 1340, 1202, 1059. ^{1}H NMR: δ 1.31 (s, 3H), 1.49 (s, 3H), 2,10 (br s, 3H), 2.70–3.08 (m, 2H), 3.38 (dd, 1H, *J* = 5.9, 3.5 Hz), 3.50 (dd, 1H, *J* = 10,8, 3.6 Hz), 3,90–4.06 (m, 1H) 4.10 (d, 1H, *J* = 10.8 Hz), 4.70 (dd, 1H, *J* = 6.2, 3.5 Hz), 4.77 (dd, 1H, *J* = 6.2, 3.6 Hz). ^{13}C NMR: δ 24.7, 26.2, 42.5, 69.4, 73.1, 81.2, 81.6, 83.1, 112.7. HRMS (CI) calcd for $C_9H_{18}NO_4$ $(M+H)^+$, 204.1236; found: 204.1228.

4.2.6. 3,6-Anhydro-1-(methylamino)-1-deoxy-4,5-*O*-isopropylidene-D-sorbitol 1f

Yield: 62%; white solid; mp 132.8–133.3 °C; $[\alpha]_D = -54.2$ (*c* 0.5, MeOH); $R_f = 0.14$ (eluent: CH_2Cl_2/MeOH (9/1)). IR 3330, 2982, 2929, 1452, 1381, 1372, 1207, 1163, 1077. ^{1}H NMR: δ 1.30 (s, 3H), 1.47 (s, 3H), 2.79 (s, 3H), 3.28 (dd, 1H *J* = 12.7, 3.4 Hz), 3.32 (dd, 1H, *J* = 12.7, 8.7 Hz), 3.55 (dd, 1H, *J* = 10.7, 3.5 Hz), 3.65 (dd, 1H, *J* = 6.7, 3.5 Hz), 4.04 (d, 1H, *J* = 10.7 Hz), 4.46 (ddd, 1H, *J* = 8.6, 6.8, 3.4 Hz), 4.73 (dd, 1H, *J* = 6.2, 3.5 Hz), 4.79 (dd, 1H, *J* = 6.2, 3.5 Hz), 6.5–7.0 (br s, 2H). ^{13}C NMR: δ 24.4, 25.9, 33.7, 51.2, 66.4, 72.6, 80.1, 82.6, 82.6, 112.4. HRMS (CI) calcd for $C_{10}H_{20}NO_4$ $(M+H)^+$, 218.1392; found, 218.1394.

4.2.7. 3,6-Anhydro-1-(isopropylamino)-1-deoxy-4,5-*O*-isopropylidene-D-sorbitol 1g

Yield: 77%; white solid; mp 103.5–104.1 °C; $[\alpha]_D = -58.8$ (*c* 1.0, CH_2Cl_2); $R_f = 0.24$ (eluent: CH_2Cl_2/MeOH (9/1)). IR 3331, 3108, 2953, 2858, 1443, 1382, 1203, 1094, 1058. ^{1}H NMR: δ 1.05 (d, 6H, *J* = 6.3 Hz), 1.30 (s, 3H), 1.46 (s, 3H), 2.2–2.5 (br s, 2H), 2.68 (ddd, 1H *J* = 11.7, 8.3, 0.9 Hz), 2.80 (sept, 1H, *J* = 6.3 Hz), 2.88 (ddd, 1H, *J* = 11.7, 3.5, 0.9 Hz), 3.35 (dd, 1H, *J* = 6.3, 3.7 Hz), 3.47 (dd, 1H, *J* = 10.7, 3.7 Hz), 4.0–4.1 (m, 2H), 4.65 (dd, 1H, *J* = 5.8, 3.7 Hz), 4.77 (dd, 1H, *J* = 5.8, 4.0 Hz). ^{13}C NMR: δ 21.8, 22.1, 23.6, 24.9, 47.7, 48.2, 68.2, 71.7, 79.7, 80.3, 82.8, 111.2. HRMS (CI) calcd for $C_{12}H_{24}NO_4$ $(M+H)^+$, 246.1705; found, 246.1710.

4.2.8. 3,6-Anhydro-1-(cyclohexylamino)-1-deoxy-4,5-*O*-isopropylidene-D-sorbitol 1h

Yield: 85%; slighly yellow crystals; mp 66–68 °C; $[\alpha]_D = -58.2$ (*c* 1.0, CH_2Cl_2); $R_f = 0.22$ (eluent: CH_2Cl_2/MeOH (95/5)). IR 3100, 2924, 2850, 1452, 1370, 1342, 1168, 1114, 1106. ^{1}H NMR: δ 1.0–1.4 (m, 8H), 1.48 (s, 3H), 1.5–2.0 (m, 5H), 2.25 (br s, 2H), 2.3–2.7 (m, 1H), 2.71 (dd, 1H, *J* = 11.8, 8.4 Hz), 2.93 (dd, 1H, *J* = 11.8, 3.6 Hz), 3.37 (dd, 1H, *J* = 6.3, 3.8 Hz), 3.48 (dd, 1H, *J* = 10.9, 3.7 Hz), 4.04 (ddd, 1H, *J* = 8.4, 6.3, 3.6 Hz), 4.09 (d, 1H, *J* = 10.9 Hz), 4,66 (dd, 1H, *J* = 6.3, 3.8 Hz), 4,78 (dd, 1H, *J* = 6.3, 3.7 Hz). ^{13}C NMR: δ 25.2, 25.3, 25.8, 26.2, 26.3, 33.4, 33.9, 48.9, 56.9, 69.1, 72.8, 81.5, 84.2, 84.5, 112.2. Anal. Calcd for $C_{15}H_{27}NO_4$: C, 63.13; H, 9.54; N, 4.91. Found: C, 63.13; H, 9.61; N, 4.79.

4.2.9. 3,6-Anhydro-1-(*tert*-butylamino)-1-deoxy-4,5-*O*-isopropylidene-D-sorbitol 1i

Yield: 69%; white solid; mp 63.5–64.5 °C; $[\alpha]_D = -62.3$ (*c* 1.0, CH_2Cl_2); $R_f = 0.34$ (eluent: CH_2Cl_2/MeOH (9/1)). IR 3459, 3312, 2958, 2922, 2854, 1456, 1380, 1358, 1206, 1095. ^{1}H NMR: δ 1.10 (s, 9H), 1.32 (s, 3H), 1.48 (s, 3H), 2.1–2.4 (br s, 2H), 2.65 (dd, 1H *J* = 11.6, 8.1 Hz), 2.86 (dd, 1H, *J* = 11.6, 3.8 Hz), 3.39 (dd, 1H, *J* = 6.3, 3.7 Hz), 3.50 (dd, 1H, *J* = 10.7, 3.7 Hz), 3.90–4.0 (m, 1H), 4.09 (d, 1H, *J* = 10.8 Hz), 4.68 (dd, 1H, *J* = 6.2, 3.5 Hz), 4.78 (dd, 1H, *J* = 6.2, 3.8 Hz). ^{13}C NMR: δ 24.6, 25.9, 28.9, 44.4, 50.3, 69.5, 72.6, 80.7, 81.1, 83.7, 112.2. HRMS (CI) calcd for $C_{13}H_{26}NO_4$ $(M+H)^+$, 204.1862; found, 204.1865.

4.2.10. 3,6-Anhydro-1-[(*S*)-(1-hydroxybutan-2-ylamino)]-1-deoxy-4,5-*O*-isopropylidene-D-sorbitol 1j

Yield: 75%; white solid; mp 75.5–77.5 °C; $[\alpha]_D = -35.3$ (*c* 1.0, CH_2Cl_2); $R_f = 0.2$ (eluent: CH_2Cl_2/MeOH (95/5)). IR 3417, 3100, 2970, 2936, 1465, 1474, 1368, 1342, 1269, 1211, 1169, 1132, 1089, 1053. ^{1}H NMR: δ 0.93 (dd, 3H, *J* = 7.4 Hz), 1.32 (s, 3H), 1.49 (s, 3H), 1.4–1.6 (m, 2H), 2.2–2.5 (br s, 3H,), 2.5–2.6 (m, 1H), 2.74 (dd, 1H, *J* = 12.3, 6.8 Hz), 2.95 (dd, 1H, *J* = 12.3, 3.8 Hz), 3.34 (dd, 1H, *J* = 10.8, 3.8 Hz) 3.45 (dd, 1H, *J* = 5.9, 3.8 Hz), 3.49 (dd, 1H, *J* = 10.8, 3.7 Hz), 3.63 (dd, 1H, *J* = 10.8, 3.8 Hz), 4.07 (d, 1H, *J* = 10.8 Hz), 4.0–4.1 (m, 1H), 4.68 (dd, 1H, *J* = 6.0, 3.8 Hz), 4.79 (dd, 1H, *J* = 6.0, 3.7 Hz). ^{13}C NMR: δ 10.4, 24.5, 25.8, 30.9, 48.6, 60.4, 62.6, 69.5, 72.5, 80.5, 81.2, 83.4, 112.2. Anal. Calcd for $C_{13}H_{25}NO_5$: C, 56.71; H, 9.15; N, 5.09. Found: C, 56.48; H, 9.06; N, 4.99.

4.2.11. 3,6-Anhydro-1-[(*R*)-(1-hydroxybutan-2-ylamino)]-1-deoxy-4,5-*O*-isopropylidene-D-sorbitol 1k

Yield: 95%; white solid; mp 73–75 °C; $[\alpha]_D = -64$ (*c* 1.0, CH_2Cl_2); $R_f = 0.3$ (eluent: CH_2Cl_2/MeOH (95/5)). IR 3292, 2958, 2841, 1461, 1380, 1314, 1274, 1243, 1203, 1163, 1141, 1089. ^{1}H NMR: δ 0.93 (dd, 3H, *J* = 7.3 Hz), 1.32 (s, 3H), 1.49 (s, 3H), 1.4–1.6 (m, 2H), 2.0–2.7 (br s, 4H), 2.7–2.9 (m, 2H), 3.33 (dd, 1H, *J* = 11.1, 6.0 Hz), 3.3–3.5 (m, 1H), 3.49 (dd, 1H, *J* = 10.6, 4.0 Hz), 3.64 (dd, 1H, *J* = 10.6, 3.8 Hz), 4.08 (d, 1H, *J* = 11.1 Hz), 4.0–4.2 (m, 1H), 4.69 (dd, 1H, *J* = 6.3, 3.6 Hz), 4.80 (dd, 1H, *J* = 6.0, 3.6 Hz). ^{13}C NMR: δ 10.3, 23.9, 24.4, 25.8, 48.7, 60.3, 62.9, 69.4, 72.5, 80.6, 81.1, 83.5, 112.3. Anal. Calcd for $C_{13}H_{25}NO_5$: C, 56.71; H, 9.15; N, 5.09. Found: C, 56.31; H, 9.11; N, 4.89.

4.2.12. 3,6-Anhydro-1-(morpholino)-1-deoxy-4,5-*O*-isopropylidene-D-sorbitol 1l

Yield: 85%; white solid; mp 54.2–55.3 °C; $R_f = 0.44$ (eluent: CH_2Cl_2/MeOH; 9/1); $[\alpha]_D = -63.8$ (*c* 1.0, CH_2Cl_2). IR 3423, 2928, 2853, 1655, 1456, 1374, 1206, 1100, 1058.0 ^{1}H NMR: δ 1.31 (s, 3H), 1.48 (s, 3H), 2.40–2.45 (m, 2H), 2.47 (dd, 1H, *J* = 12.4, 9.5 Hz), 2.62 (dd, 1H, *J* = 12.4, 3.5 Hz), 2.65–2.70 (m, 2H), 3.34 (dd, 1H, *J* = 6.9, 3.5), 3.44 (br s, 1H), 3.50 (dd, 1H, *J* = 11.0, 3.8 Hz), 3.6–3.7 (m, 4H), 4.08 (d, 1H, *J* = 11.0 Hz), 4.11 (m, 1H, *J* = 9.5, 6.9, 3.5 Hz), 4.65 (dd, 1H, *J* = 6.2, 3.5 Hz), 4.79 (dd, 1H, *J* = 6.2, 3.8 Hz). – ^{13}C NMR: δ 24.7, 26.0, 53.9, 60.5, 66.5, 67.0, 72.7, 80.6, 81.3, 84.1, 112.3. HRMS (CI) calcd for $C_{13}H_{24}NO_5$ $(M+H)^+$, 274.1654; found, 274.1662.

4.3. General procedure for the asymmetric transfer hydrogenation of acetophenone

A Schlenk tube equipped with a stirrer bar was charged with benzeneruthenium(II) chloride dimer (3.5 mg, 7 μmol) and ligand **1a** (8.2 mg, 28 μmol). The mixture was then degassed and freshly dried, and degassed propan-2-ol (3 mL) was added under argon. The solution was heated at 70 °C for 1 h. After cooling the mixture to room temperature, it was diluted with propan-2-ol (4 mL) and *t*-BuOK (280 μL, 0.1 M in propan-2-ol) was added. The resulting solution was stirred for 10 min before acetophenone (165 μL, 1.4 mmol) was added. The reaction mixture was stirred at 70 °C for 21 h. The conversion and ee were determined by chiral GC (Restek β-dex sm (30 m × 0.25 mm × 0.25 μm, gaz: He constant flow 3.4 mL/min, 120 °C (0.5 min) then 0.6 °C/min until 125 °C (1 min)): t_R = 6.07 (*R* major), 6.33 (*S* minor)). $[\alpha]_D$ = +35.6 (c 1.03, CH_2Cl_2) (1-phenylethanol isolated from entry 16, Table 2).

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